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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,668	01/27/2004	David B. Rozema	25775 US1	9890

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EXAMINER	
DUNSTON, JENNIFER ANN	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
04/27/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,668	ROZEMA ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,7,12 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,7,12 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 1/13/2010, in which claims 8, 17, 21 and 22 were canceled. Claims 5, 7, 12 and 16 are pending and under consideration.

Any rejection of record in the previous office actions not addressed herein is withdrawn. New grounds of rejection are presented herein that were not necessitated by applicant's amendment of the claims since the office action mailed 10/2/2009. Therefore, this action is not final.

Specification

The disclosure is objected to because of the following informalities:

1. At page 6, line 25, the phrase "for delivery of the" should be removed from the sentence to improve the grammar.

2. At page 6, line 7, the word "delivery" should be replaced with "deliver" to improve the grammar.

3. At page 15, line 12, the term "SEQ ID 1" should be replaced with "SEQ ID NO: 1." Where the description or claims of a patent application discuss a sequence that is set forth in the Sequence Listing, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID **NO:**" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. See 37 CFR 1.821(d).

Appropriate correction is required.

Response to Arguments - Claim Objections

The objections to claims 8, 17, 21 and 22 are moot in view of Applicant's cancellation of the claims in the reply filed 1/13/2010.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffman et al (US Patent No. 6,835,393 B2; see the entire reference) in view of Oda et al (Journal of the National Cancer Institute, Vol. 79, No. 6, pages 1205-1211, 1987, cited on the IDS filed 10/4/2004; see the entire reference). This is a new rejection.

Claim 5 is drawn to a process for delivering a polynucleotide to the cytoplasm of a cell *in vitro* consisting of (a) forming a styrene-maleic anhydride random copolymer; (b) increasing hydrophobicity of the copolymer by randomly attaching hydrophobic groups along the copolymer backbone in a sufficient amount to form a membrane active polyanion capable of lysing mammalian cell membranes at pH 6.5 wherein randomly attaching hydrophobic groups along the copolymer backbone consists of reacting hydrophobic amines or hydrophobic alcohols with anhydride monomers in the copolymer; and (c) contacting said cell with said polynucleotide and said membrane active polyanion such that the polynucleotide and the membrane active polyanion are endocytosed by the cell. Claim 7 depends from claim 5 and limits the hydrophobic amines to alkyl amines. Claim 7 does not further limit the hydrophobic alcohols of the method. With regard to step (c) of the method, the specification teaches that contacting a cell with a polynucleotide and a membrane active polymer such that the polynucleotide and polymer are endocytosed by the cell is performed (i) where the polynucleotide and polymer are not associated with each other but are both endocytosed by the cell; (ii) where the polynucleotide and polymer are associated with each other by non-covalent interactions; or (iii) where the polynucleotide and polymer are associated with each other by covalent interactions (e.g., page 6, lines 23-30).

Hoffman et al teach method for the transport of compounds through cell layers or barriers and release of the compounds, such as oligonucleotides, within cells by administering to a cell *in vitro* a composition that includes a compound that disrupts endosomal membranes in response to low pH in the endosomes but which are relatively inactive toward cell membranes, coupled directly or indirectly to the compound (e.g., Abstract; paragraph bridging columns 3-4; column

17, lines 5-24; claims 1, 4 and 5). Hoffman et al teach that the endosomal membrane disrupting compounds are most preferably pH sensitive polymers that are inert at physiological pH (around pH 7.4) but which disrupt the endosomal membrane at the pH range inside the endosome (between about 5.1 and 5.5) (e.g., column 4, lines 10-15; column 6, lines 33-41). More specifically, Hoffman et al teach that any polymer can be used which is not hydrophobic at physiological pH, typically in the range of between 6.8 and 7.5, and approximately 7.4 inside cells, but which becomes hydrophobic at the pH inside the endosomes (between 5.0 and 6.5) (e.g., column 6, lines 42-46). Such polymers include multiple carboxylic acid groups, such as polymers with more than 0.5 carboxylic acid groups per monomer on average, which tend to be relatively hydrophilic at pH ranges in which the carboxylic acid groups are deprotonated, and tend to be relatively hydrophobic at pH ranges in which the carboxylic acid groups are protonated (e.g., column 6, lines 46-54).

Hoffman et al does not teach the method where the pH sensitive polymer is provided by forming a styrene-maleic anhydride random copolymer, and reacting hydrophobic alcohols with anhydride monomers in the copolymer.

Oda et al teach a process consisting of a) forming a styrene-maleic anhydride random copolymer (SMA); b) reacting 50-70% (mol/mol) of the carboxyl groups of maleic acid with butyl alcohol to form a butyl ester derivative of SMA; c) conjugating the butyl ester SMA with the drug neocarzinostatin (NCS) to form SMANCS; and d) contacting a cell *in vitro* with the SMANCS such that the SMANCS is endocytosed by the cell (e.g., paragraph bridging pages 1205-1206page 1206, right column, last full paragraph; page 1209, right column, full paragraph; page 1210, paragraph bridging columns). Oda et al teach that compounds internalized into cells

by endocytosis are found in intracellular acidic vesicles before being fused with lysozomes, and an acidic environment may greatly affect the state of the carboxyl group of both NCS (total of 14 residues) and SMANCS (at least 28 residues) (e.g., page 1209, Discussion). Oda et al teach that, in the acidic environment, the carboxyl groups become more hydrophobic, thus favoring interaction with the lipid bilayer of the cell membrane, resulting in inversion of the carboxyl groups into the membrane and penetration of the drugs into the cytoplasm (e.g., page 1209, Discussion).

Both Hoffman et al and Oda et al teach the use of polymers to deliver a molecule to the cytoplasm of a cell *in vitro*. Hoffman et al teaches the use of any pH sensitive polymer that contains carboxyl groups that become protonated in the endosome, and Oda et al teach the use of butyl ester derivative of styrene maleic acid anhydride random copolymer (butyl SMA) for the delivery of a drug to a cell *in vitro* where the polymer contains carboxyl groups that become protonated in the endosome. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the butyl SMA of Oda et al for the pH sensitive polymer of Hoffman et al in order to achieve the predictable result of using butyl SMA to improve the delivery of a polynucleotide to a cell *in vitro*.

Claims 12 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffman et al (US Patent No. 6,835,393 B2; see the entire reference) in view of Saettone et al. ("Inserts for Sustained Ocular Delivery of Pilocarpine: Evaluation of a Series of Partial Esters of (Maleic Acid – Alkyl Vinyl Ether) Alternating Copolymers." Polymers in Medicine III: Third International Conference on Polymers in Medicine, Porto Cervo Italy, Ed. Migliarese, C., et al.

Elsevier Science Publishers B.V., pages 209-224, 1998, cited in a prior action; see the entire reference). This is a new rejection.

Claim 12 is drawn to a process for delivering a polynucleotide to the cytoplasm of a cell *in vitro* consisting of (a) forming a butyl vinyl ether-maleic anhydride alternating copolymer; (b) increasing hydrophobicity of the copolymer by randomly attaching hydrophobic groups along the copolymer backbone in a sufficient amount to form a membrane active polyanion capable of lysing mammalian cell membranes at pH 6.5 wherein randomly attaching hydrophobic groups along the copolymer backbone consists of reacting hydrophobic amines or hydrophobic alcohols with anhydride monomers in the copolymer; and (c) contacting said cell with said polynucleotide and said membrane active polyanion such that the polynucleotide and the membrane active polyanion are endocytosed by the cell. Claim 16 depends from claim 12 and limits the hydrophobic amines to alkyl amines. Claim 16 does not further limit the hydrophobic alcohols of the method. With regard to step (c) of the method, the specification teaches that contacting a cell with a polynucleotide and a membrane active polymer such that the polynucleotide and polymer are endocytosed by the cell is performed (i) where the polynucleotide and polymer are not associated with each other but are both endocytosed by the cell; (ii) where the polynucleotide and polymer are associated with each other by non-covalent interactions; or (iii) where the polynucleotide and polymer are associated with each other by covalent interactions (e.g., page 6, lines 23-30).

Hoffman et al teach method for the transport of compounds through cell layers or barriers and release of the compounds, such as oligonucleotides, within cells by administering to a cell *in vitro* a composition that includes a compound that disrupts endosomal membranes in response to

low pH in the endosomes but which are relatively inactive toward cell membranes, coupled directly or indirectly to the compound (e.g., Abstract; paragraph bridging columns 3-4; column 17, lines 5-24; claims 1, 4 and 5). Hoffman et al teach that the endosomal membrane disrupting compounds are most preferably pH sensitive polymers that are inert at physiological pH (around pH 7.4) but which disrupt the endosomal membrane at the pH range inside the endosome (between about 5.1 and 5.5) (e.g., column 4, lines 10-15; column 6, lines 33-41). More specifically, Hoffman et al teach that any polymer can be used which is not hydrophobic at physiological pH, typically in the range of between 6.8 and 7.5, and approximately 7.4 inside cells, but which becomes hydrophobic at the pH inside the endosomes (between 5.0 and 6.5) (e.g., column 6, lines 42-46). Such polymers include multiple carboxylic acid groups, such as polymers with more than 0.5 carboxylic acid groups per monomer on average, which tend to be relatively hydrophilic at pH ranges in which the carboxylic acid groups are deprotonated, and tend to be relatively hydrophobic at pH ranges in which the carboxylic acid groups are protonated (e.g., column 6, lines 46-54).

Hoffman et al does not teach the method where the polyanion is provided by forming a butyl vinyl ether maleic anhydride alternating copolymer, and reacting hydrophobic alcohols with anhydride monomers in the copolymer.

Saettone et al teach the synthesis of butyl vinyl ether-maleic anhydride alternating copolymer, and the reaction of anhydride moieties of the copolymer with hydrophobic alcohol (e.g., page 221, section a2) Polymers; page 214Table 1). Saettone et al specifically teach the methyl ester of butyl vinyl ether maleic anhydride (M-BVEMA), which was 40% esterified or 54% esterified (e.g., Table 1; page 214). Saettone et al teach contacting a cell with M-BVEMA

and pilocarpine base (PiB, a drug) (e.g., pages 211-212, section b) preparation of the inserts). Saettone et al teach that 54% esterified M-VBEMA significantly increased delivery of the drug to cells (e.g., pages 218-220, section b3) Biological tests; Figure 4). Saettone et al teach that alkyl half esters of (maleic acid – alkyl vinyl ether) copolymers are attractive materials for drug delivery on account of their widespread acceptance in pharmaceutical preparations, and of the possibility of varying their structural characteristics by simple chemical modifications occurring at the level of the anhydride group (e.g., paragraph bridging pages 220-221).

Both Hoffman et al and Saettone et al teach the use of polymers to deliver a molecule to the cytoplasm of a cell *in vitro*. Hoffman et al teaches the use of polymers that are pH sensitive, which include multiple carboxylic acid groups that tend to be relatively hydrophilic at pH ranges in which the carboxylic acid groups are deprotonated and tend to be relatively hydrophobic at pH ranges in which the carboxylic acid groups are protonated (e.g., the endosome), and Saettone et al teach the use of a methyl ester of butyl vinyl ether maleic anhydride alternating copolymer (M-BVEMA), which has the characteristics described by Hoffman et al. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the M-BVEMA of Saettone et al as the pH sensitive polymer of Hoffman et al in order to achieve the predictable result of using M-BVEMA to improve the delivery of a polynucleotide to a cell *in vitro*.

Where the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of the claimed product. See *In re Ludtke* 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the

rejection is based on "inherency" under 35 U.S.C. 102, or "prima facie obviousness" under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). In the instant case, the methyl ester of butyl vinyl ether maleic anhydride alternating copolymer of Saettone et al is identical to the compound disclosed as M-BVEMA in the present specification. M-BVEMA is disclosed as having the ability to lyse mammalian cell membranes at pH 6.5 (e.g., Figure 3).

Response to Arguments - 35 USC § 103

The rejection of claims 8 and 21 under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 01/49841) in view of Oda et al (Journal of the National Cancer Institute, Vol. 79, No. 6, pages 1205-1211, 1987) is moot in view of Applicant's cancellation of the claims in the reply filed 1/13/2010.

The rejection of claims 17 and 22 under 35 U.S.C. 103(a) as being unpatentable over Wolff (WO 01/49841) in view of Saettone et al is moot in view of Applicant's cancellation of the claims in the reply filed 1/13/2010.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Examiner
Art Unit 1636